PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-476/WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/HR 03/00036	International filing date *(day/month/year)* 07.07.2003	Priority date *(day/month/year)* 19.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D213/74		
Applicant PLIVA D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.02.2004	29.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Scruton-Evans, I Telephone No. +49 89 2399-8272

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HR 03/00036

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-6 as originally filed

Claims, Numbers

1-15 received on 18.10.2004 with letter of 11.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

D1: WO 01/10441 A (DOLITZKY BEN ZION ;KORDOVA MARKO (IL); TEVA PHARMA (IL); ARONHIME) 15 February 2001 (2001-02-15)

D2: US-A-6 166 045 (BURGER ARTUR ET AL) 26 December 2000 (2000-12-26)

D3: ROLLINGER J M ET AL: "Crystal forms of torasemide: new insights" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 53, no. 1, January 2002 (2002-01), pages 75-86, XP004331334 ISSN: 0939-6411

D4: US-A-4 743 693 (TOPFMEIER FRITZ ET AL) 10 May 1988 (1988-05-10)

D5: WO 00/20395 A (PLIVA FARMACEUTSKA IND DIONI &) 13 April 2000 (2000-04-13)

With regard to the requirement for novelty, the claims have been amended such that the controlled acidifying is carried out by continuous addition of acid at room temperature or about it. This has support in the application as originally filed, page 4, 2nd paragraph. Novelty can be formally acknowledged re D3 and D5 on account of these features being included into the claim 1 (Article 33(2) of the PCT):

With regard to the requirement for inventive step (Article 33(3) of the PCT), the advantages stated in the description, page 3, paragraph 4 could form the basis of an inventive step if they were substantiated by actual comparative data.

Claims

1. Process for the preparation of modification I of torasemide, characterized in that an alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide is subjected to controlled acidifying with inorganic or organic acid by continuous addition of said acid at room temperature or about it.

2. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I of torasemide is chemically pure.

3. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I of torasemide contains less than 0.5 % of water.

4. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the modification I contains remaining solvents within pharmacopeic limits.

5. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for the preparation of the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide water solutions of lithium, sodium and potassium hydroxide and water solutions of sodium and potassium carbonate are used.

6. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for acidifying the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide inorganic acids such as hydrochloric, sulfuric, phosphoric and nitric acids or organic acids such as formic, acetic, propionic, oxalic, tartaric, methanesulfonic or *p*-toluenesulfonic acid are used.

7. Process for the preparation of modification I of torasemide according to claim 1, characterized in that for acidifying the alkaline extract of the original reaction mixture of the last phase in the synthesis of torasemide carbon dioxide is used.

8. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out up to a pH from about 8.5 to about 5.0.

9. Process for the preparation of modification I of torasemide according to claim 8, characterized in that the acidifying is carried out up to a pH from about 7.5 to about 7.0.

10. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out at a stirrer rate from 10 r/min to 300 r/min.

11. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out within 5 minutes to 24 hours.

12. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the acidifying is carried out without avoiding high local acid concentrations.

13. Process for the preparation of modification I of torasemide according to claim 1, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred from 10 minutes to 240 minutes.

14. Process for the preparation of modification I of torasemide according to claim 13, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred at a temperature from 0 °C to 50 °C.

15. Process for the preparation of modification I of torasemide according to claim 14, characterized in that the suspension obtained after acidifying and reaching the desired pH is stirred at room temperature.